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Merging of Light/Dark Palladium Catalytic Cycles Enables Multicomponent Tandem Alkyl Heck/Tsuji–Trost Homologative Amination Reaction toward Allylic Amines

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Abstract

A visible light-induced palladium-catalyzed homologative three-component synthesis of allylic amines has been developed. This protocol proceeds *via* a unique mechanism involving two distinct cycles enabled by the same Pd(0) catalyst: a visible light-induced hybrid radical alkyl Heck reaction between 1,1-dielectrophile and styrene, followed by the “in dark” classical Tsuji–Trost-type allylic substitution reaction. This method works well with a broad range of primary and secondary amines, aryl alkenes, dielectrophiles, and in complex settings. The regiochemistry of the obtained products is primarily governed by the structure of 1,1-dielectrophile. Involvement of π-allyl palladium intermediates allowed for the control of stereoselectivity, which has been demonstrated with up to 95:5 er.

Graphical Abstract

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Supporting Information

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Additional experimental details, materials, methods, and characterization data for all new compounds (PDF)

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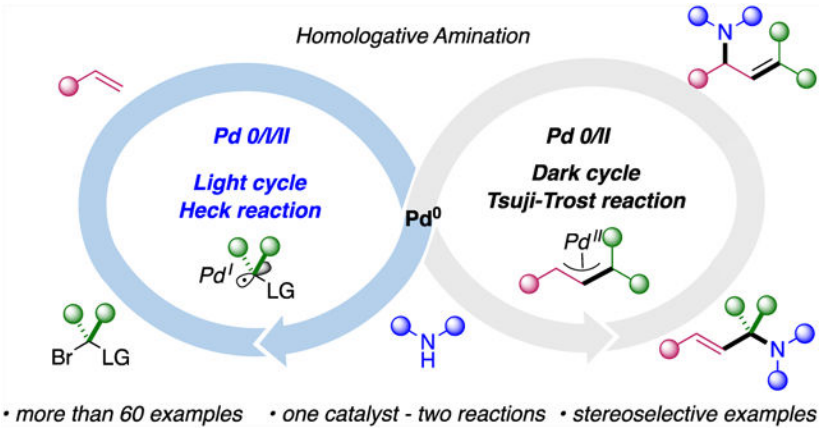

1. INTRODUCTION

It is hard to overstate the importance of amine functionality in bioactive molecules and drugs.[1] The allylic amine motif is one of the privileged fragments found in these molecules (Scheme 1a). Traditionally, allylic amines are synthesized *via* substitution reactions or reductive amination protocols.[2] However, these operationally simple methods suffer from several drawbacks, including over-substitution side reaction, lack of stereocontrol, and necessity to employ highly reactive reagents. These problems hamper the use of the aforementioned methods for the construction of complex or densely substituted molecules.

Accordingly, the development of general and efficient methods toward allylic amines from various precursors has been extensively explored.[3] Arguably, the Pd-catalyzed Tsuji–Trost reaction is one of the most powerful modern approaches toward allylic amines, which allows for mild and general construction of allylic amines with high degrees of regio- and stereocontrol (Scheme 1b **I**).[4] In this protocol, the range of leaving groups is significantly expanded compared to that in classical substitution reactions.[5] A newer version of this approach expanded the range of electrophilic components of this reaction to 1,3-dienes (**II**).[6] Probably, one of the most important modern developments of the π-allyl palladium amination chemistry relies on the C–H functionalization approach (**III**).[7] Under this more atom-economic scenario, the amination of non-prefunctionalized allylic C–H bonds greatly increases the pool of substrates. This direction has gained attention recently[8] with the discovery of alternative mechanistic approaches in palladium catalysis (**IV**).[9] Nonetheless, all current π-allyl palladium approaches toward allylic amines rely on a certain chemical space, revolving around allylic electrophiles possessing a leaving group at the allylic position (**I**), a diene moiety (**II**), or an allylic C–H bond (**III**, **IV**). Assembling allylic amines from different types of electrophiles diversifies the range of tools available to synthetic and medicinal chemists toward these important motifs. In this light, homologative synthesis of amines directly from alkenes, which do not possess an allylic moiety, is a valuable alternative (Scheme 1c). Thus, MacMillan introduced a photocatalytic method toward allylic amines, proceeding *via* the radical addition/elimination pathway.[10] Although it requires a pre-functionalized alkene, employment of various tertiary amines, as well as amino acid derivatives, allows for synthesis of branched products. Huang reported an elegant route

toward allylic amines *via* the Heck-type C–H alkylation reaction of styrenes with aminals.[11] This approach does not require pre-functionalization of alkene; however, it is restricted to the methylene-substituted aminals, which limits the scope of the obtained products to linear allylic amines. Moreover, the aminal route precludes the use of primary amines in this transformation. Although these homologative methods (Scheme 1c) expand the scope of allylic amine precursors, they share a two-component C–C bond disconnection logic, which leaves out the possibility of engaging a large and diverse feedstock of primary and secondary amines.

To address the aforementioned limitations, we propose an alternative approach toward allylic amines, which relies on a homologative three-component assembly of allylic amines from vinyl arenes and heteroarenes, primary or secondary amines, and dielectrophiles. This mild method proceeds *via* unique for Pd chemistry dual catalytic cycle, including *light-induced* Pd 0/I/II cycle and a traditional "*dark*" Pd 0/II manifold. Importantly, this approach, which presumes a new three-component route to the key π-allyl palladium intermediate, gives access to branched allylic amines, including complex and bioactive molecules, and offers opportunity toward diastereo- and enantioselective versions of this reaction (Scheme 1d).

2. REACTION DESIGN

In 2017, our group disclosed a visible light-induced Pd-catalyzed alkyl Heck reaction between structurally diverse alkyl halides and vinyl arenes.[12] The success of this transformation relied on a novel activation mode of electrophiles, involving formation of hybrid Pd-radical intermediates. The follow-up reports from our group and others have significantly expanded this chemistry and types of electrophiles used.[13] We hypothesized that this platform could be applied to some 1,1-dielectrophiles, which could engage in the alkyl Heck-type transformation for the *in situ* generation of an allylic intermediate *i*, a capable precursor for a subsequent Tsuji–Trost amination step. Considering that the conditions for the alkyl Heck and Tsuji–Trost reactions could be similar in terms of requisite Pd precursors and ligands, we hoped to achieve both transformations using a single catalyst system.

3. RESULTS AND DISCUSSION

3.1. Reaction Optimization.

Study commenced with identifying capable dielectrophiles. Attempts at employing dibromomethane in the reaction with styrene and piperidine under blue light irradiation in the presence of the $Pd(PPh_3)_4$ catalyst (Table 1, entry 1) resulted in exclusive formation of aminal **3′**, a product of the double S_N2 alkylation reaction. We embarked on solving this problem by employment of sterically more congested α-halomethyl ammonium salts **4**–**9**. These dielectrophiles seemed promising for the designed transformation since α-halomethyl ammonium salts were previously used for generation of radical species by homolysis of the C–halogen bond.[14] Moreover, allylic ammonium salts, the expected intermediates of the first step of the sequence, are prominent electrophiles for the Tsuji–Trost reaction.[15] Gratifyingly, employment of DABCO-derived salt **4** led to formation of the desired product **3**, albeit in low yield (entry 2). Further optimization revealed that structurally simpler salt **5** can also

be employed in this reaction (entry 3). DPEPhos appeared to be the most effective ligand (entry 5) and diisorpopylamine (DIPA) the most effective base (entry 6, ***Conditions A***). A control experiment revealed that light was crucial for this transformation (entry 7). Use of structurally varied ammonium salts **7**–**9**, including a diiodomethane-derived compound (**9**), resulted in similar outcomes under standard conditions (entry 8). Salt **5** was chosen as a benchmark dielectrophile for introduction of the methylene unit due to the ease of preparation as well as due to the volatility of the trimethylamine byproduct.

Next, potential use of substituted dielectrophiles was explored. Gratifyingly, homologues of dibromomethane, such as 1,1-dibromoethane, did not suffer from double S_N2 alkylation reaction. However, the reaction conditions optimal for ammonium salts have proven to be ineffective for dibromides (entry 9). Performing the reaction in 1,4-dioxane somewhat improved the yield (entry 10). Ligand screening revealed that triphenylphosphine did not promote the desired transformation (entry 11), whereas switching to Xantphos dramatically improved the reaction outcome (entry 12). Notably, formation of the minor regioisomeric allylamine **3″** was also observed. The selectivity of amination was improved under more diluted conditions (entry 13, ***Conditions B***). A control experiment revealed that light is crucial for this transformation (entry 14). Attempts to use geminal diiodide **10** resulted in complete decomposition of the starting material (entry 15), whereas dichloride **11** remained intact (entry 16).

3.2. Substrate Scope.

Evaluation of substrate scope began with testing various primary and secondary amines in reaction with ammonium salt **5** and styrene under ***Conditions A*** (Scheme 2). Employment of basic amines resulted in good yields of products (**12**–**15**). Use of HCl salt of piperidine was also successful, albeit with marginal loss in efficiency (**14**, 72 *vs* 66%). Gratifyingly, this reaction showed wide functional group tolerance, as variably substituted amines reacted uneventfully (**16**–**23**). Importantly, alkyl chloride-containing product **17** was synthesized without compromising the C–Cl bond, which otherwise was demonstrated under light-induced Pd-catalyzed reactions.[16] Employment of a weak amine base ensures that base-sensitive functions such as ketone (**16**), sulfone (**20**), and secondary amide (**23**) do not form alternative nucleophilic centers. Amino acid derivatives turned out to be capable reaction partners to deliver the corresponding allyl amine products **26** and **27** in reasonable yields. Importantly, this three-component allylic amination reaction performed well with complex densely substituted amines (**28**–**34**). Of note, under ***Conditions A***, the products derived from small-ring nitrogen-containing heterocycles, such as aziridine and azetidine, where not stable. Potentially, in the polar medium, ring-opening reactions may lead to the decomposition of the products. However, these products can be obtained under ***Conditions B*** (**35**, **36**). Primary amines can equally efficiently be used under both conditions (**37**, **39**).

Next, the scope of alkenes was studied (Scheme 3). Under ***Conditions A***, electron-rich vinyl arenes(heteroarenes) (**40**, **41**, **43**, **44**, **46**) reacted smoothly, whereas their electro-poor counterparts were less reactive (**42**, see the Supporting Information for additional details). Apparently, this reactivity trend can be attributed to high electrophilicty of the formed methylene ammonium radical intermediate.[14] Complementarily, the reactions

with 1,1-dibromoethane, which is the precursor for more nucleophilic α-bromo carbon centered radical (***Conditions B***),[17] were more effective with electron-deficient vinyl arenes(heteroarenes) (**48**, **49**, **50**, **52**, **53**). The robustness of this protocol was highlighted by efficient carboamination of structurally complex alkenes (**47**, **54**, **56**, **57**). Notably, albeit with moderate efficiency, indene can also be engaged in this transformation (**45**). Attempts to perform this reaction intermolecularly with unactivated olefins have been unsuccessful, so far.

Upon study of 1,1-dielectrophiles (Scheme 4), it was shown that employment of deuterated ammonium salt **58** allows for accessing deuterated piperidine derivative **59** as well as deuterated naftifine (**60**). 1,1-Dibromoethane (**61**) performed well with both cyclic and acyclic amines, resulting in products **62**[18] and **63**, respectively. Furthermore, it was discovered that in reactions with a weak aniline nucleophile under ***Conditions B***, geminal bromoacetate **64**[19] can also be employed as a dielectrophile to deliver product **38** in moderate yield. Dibromide **65** containing longer alkyl chains also gave the desired product **66**, albeit in diminished yield. When employing dielectrophile **67** containing a benzoate group, product **68** was obtained as a mixture of regioisomers with amine attached to a benzylic position in the major isomer. Apparently, the observed switch of selectivity of amination is governed by sterics. This effect was further exposed in the formation of products **70** and **72**, where additional substituents shifted regioselectivity completely. The same outcome was observed employing (dibromomethyl)trimethylsilane (**73**), which led to **74**, an ambiphilic molecule possessing allylic amine and vinyl silane moieties. 2,2-Dibromo-1,1,1-trifluoroethane (**75**) also yielded benzylic amine **76**, an expected product of the Tsuji–Trost reaction.[20] Given that intermolecular alkylamination with unactivated alkenes so far was unsuccessful, the intramolecular version was tested. Expectedly, two-component reaction of allylsilyl ether **77**[21] with piperidine underwent 1,5-*exo*trigcyclization followed by allylic substitution to produce **78** in reasonable yield. In contrast to dibromide electrophiles, geminal diiodides were incompatible with the reaction conditions. However, the corresponding dichloride proved to be a capable reaction partner under slightly modified conditions (**79** → **66**).

After establishing this three-component coupling strategy with dielectrophiles, amines, and styrenes, the possibility of engagement of electron-deficient alkenes, such as acrylic esters and amides, in this transformation was explored (Scheme 5). Obviously, due to polarity matching,[17] these alkenes prefer to react with nucleophilic radicals. It was found that bromo acetates, the precursors of the relatively nucleophilic α-acetoxy *C*-centered radical, could be viable substrates for this reaction. Thus, bromoacetate **64** smoothly reacted with acrylic esters (**80**, **82**) and amides (**83**–**87**), including those under more complex settings (**85**, **87**). The corresponding dibromide can also be engaged in the reaction (**81**) though with a lower efficiency. However, less reactive amines, such as anilines (**80**, **82**–**88**) or *tert*-butylamine (**81**), must be employed in this reaction to prevent premature Michael addition.

Next, the feasibility of inducing a stereocontrol has been validated (Scheme 5). Understandably, substituted dibromide electrophiles, which allowed for introduction of a stereogenic center at the allylic position, were employed. First, a diastereoselective version

of this reaction employing a chiral amine component was examined under slightly modified conditions[22] to those previously developed for allylic C–H amination reaction[8] (Scheme 6a, ***conditions C***). Thus, several amino acids derivatives underwent smooth three-component coupling reaction with styrene and 1,1-dibromoethane or 1,1-dibromopropane to afford allylic amines **88**–**91** with good stereocontrol. Note that a chiral ligand must be employed to achieve reasonable diastereocontrol as use of Xantphos leads to low selectivity (**89**). Naturally, a much more significant, enantioselective version of this reaction was explored next (Scheme 6b). *Gratifyingly, it was found that under* ***conditions D*** *enantiocontrol of up to 95:5 er could be achieved!* Experiments indicated that under these conditions, employment of dibromide possessing a longer alkyl chain (**65**) was essential for achieving high enantioselectivity. Primary isopropylamine (**92**–**96**) and benzylamine (**97**) were efficient. Likewise, secondary acyclic (**98**, **99**) and cyclic amines (**100**) were also capable reaction partners. The enantioselectivity of this reaction was not sensitive to the electronic factors at vinyl arenes (**92**–**95**). However, employment of electron-rich substrates diminished the regioselectivity (**93**, **94**).

3.3. Mechanistic Investigations.

By design, this tandem reaction expected to proceed *via* the alkyl-Heck reaction first. However, monitoring the reaction profile revealed no detectable products of this reaction. This outcome may be rationalized in terms of the higher rates of the subsequent Tsuji–Trost substitution reaction step, thus preventing the buildup of the first step intermediate. This assumption was validated by the following experiment (Scheme 7). α-Methyl styrene **101** was subjected to the standard reaction conditions (***Conditions B***), which was expected to result in homoallylic bromide **102** *via* a more facile β-H elimination from the less hindered site of *v*.[21,23] Indeed, **102** was obtained in 30% NMR yield, thus supporting the above assumption. Subjecting cinnamyl electrophiles **103** to reaction with piperidine (**2**) even in the absence of light validated a rapid rate of Tsuji–Trost substitution as quantitative formation of product **104** was observed within 5 min.[24] Additionally, a radical probe experiment with cyclopropyl-containing styrene **105** led to a radical cyclization product **106** *via* radical addition/ring opening/cyclization sequence. This result not only validates the initial alkyl Heck reaction but also supports the radical nature of the reaction. The presence of radicals was further verified by TEMPO- and spin-trapping experiments.[22] The above data validate consecutive involvement of two different cycles catalyzed by the same Pd catalyst: the light-induced cycle and the thermal cycle. A combination of two distinct light/dark catalytic cycles has been reported.[25] However, in all these cases, in the light cycle, the transition metal serves as a photocatalyst, either *via* SET or energy transfer, thus not participating in the bond breaking/forming event. To the best of our knowledge, cases where the same transition-metal catalyst performs two different catalytic reactions in light and dark cycles are unprecedented. Based on the above mechanistic experiments and literature reports,[12,13] the following mechanism was proposed for this three-component homologative amination reaction. It begins with the SET from photoexcited Pd(0) complex to a dielectrophile to generate a hybrid Pd(I)/radical species **A**. A subsequent radical addition (**B**) and β-H elimination (“Heck cycle”) produces intermediate (**INT**) and recovers the Pd(0) catalyst. Then, both are engaged in the second, “Tsuji–Trost cycle” to generate π-allyl Pd complex **D**, which upon nucleophilic attack leads to an allylic amine product

(**PR**). The regioselectivity of substitution is governed primarily by the structure of π-allyl complex substituents and nature of the amine.

4. CONCLUSIONS

In summary, we developed a protocol for rapid homologative assembly of allylic amines from alkenes, dielectrophiles, and amines under mild visible light-induced Pd-catalyzed conditions. This reaction operates *via* unprecedented merging of light/dark catalytic cycles performed by the same Pd(0) species. Wide variability of the reaction partners enables access to a broad range of differently substituted allylic amines, including complex compounds, which would be difficult to access *via* previously reported protocols. Initial attempts indicated the feasibility to perform this transformation in diastereo- and enantiocontrolled fashion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(20). (a)Kawatsura M; Hirakawa T; Tanaka T; Ikeda D; Hayase S; Itoh T Regioselective Synthesis of Trifluoromethyl Group Substituted Allylic Amines via Palladium-Catalyzed Allylic Amination. Tetrahedron Lett. 2008, 49, 2450–2453.(b)Hirakawa T; Ikeda K; Ikeda D; Tanaka T; Ogasa H; Kawatsura M; Itoh T Regioselective Synthesis of Trifluoromethyl Group Containing Allylic Amines by Palladium-Catalyzed Allylic Amination and Sequential Isomerization. Tetrahedron 2011, 67, 8238–8247.

(21). For intramolecular alkyl-Heck reaction of silyl methyl halides, see: Parasram M; Iaroshenko VO; Gevorgyan V Endo-Selective Pd-Catalyzed Silyl Methyl Heck Reaction. J. Am. Chem. Soc 2014, 136, 17926–17929. [PubMed: 25494921]

(22). See Supporting Information for details.

(23). (a)Parasram M; Chuentragool P; Wang Y; Shi Y; Gevorgyan V General, Auxiliary-Enabled Photoinduced Pd-Catalyzed Remote Desaturation of Aliphatic Alcohols. J. Am. Chem. Soc 2017, 139, 14857–14860. [PubMed: 28992686] (b)Chuentragool P; Parasram M; Shi Y; Gevorgyan V General, Mild, and Selective Method for Desaturation of Aliphatic Amines. J. Am. Chem. Soc 2018, 140, 2465–2468. [PubMed: 29400959]

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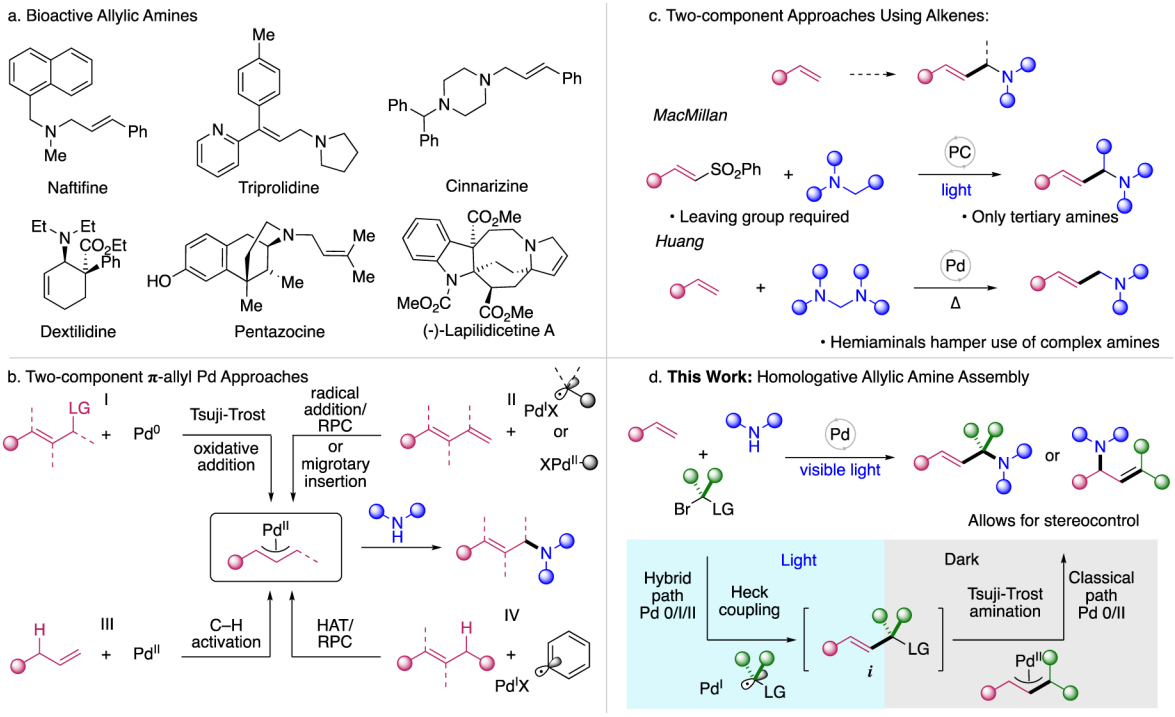
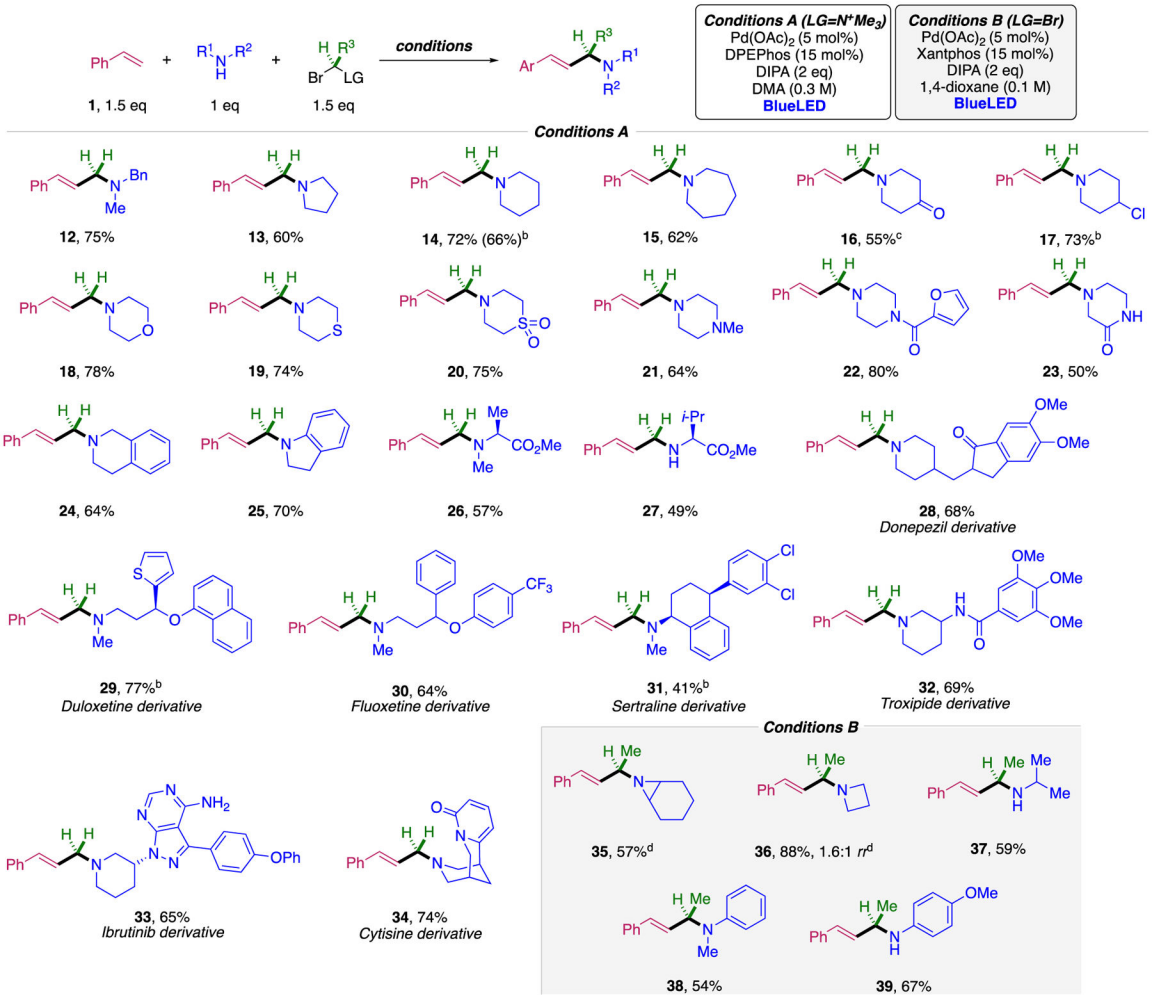
(25). (a)Huo H; Shen X; Wang C; Zhang L; Röse P; Chen L-A; Harms K; Marsch M; Hilt G; Meggers E Asymmetric Photoredox Transition-Metal Catalysis Activated by Visible Light. Nature 2014, 515, 100–103. [PubMed: 25373679] (b)Lei W-L; Wang T; Feng K-W; Wu L-Z; Liu Q Visible-Light-Driven Synthesis of 4-Alkyl/Aryl-2-Aminothiazoles Promoted by In Situ Generated Copper Photocatalyst. ACS Catal. 2017, 7, 7941–7945.(c)Han B; Li Y; Yu Y; Gong L Photocatalytic Enantioselective α-Aminoalkylation of Acyclic Imine Derivatives by a Chiral Copper Catalyst. Nat. Commun 2019, 10, 3804. [PubMed: 31444326] (d)Li Z; Wang

X; Xia S; Jin J Ligand-Accelerated Iron Photocatalysis Enabling Decarboxylative Alkylation of Heteroarenes. Org. Lett 2019, 21, 4259–4265. [PubMed: 31090423]



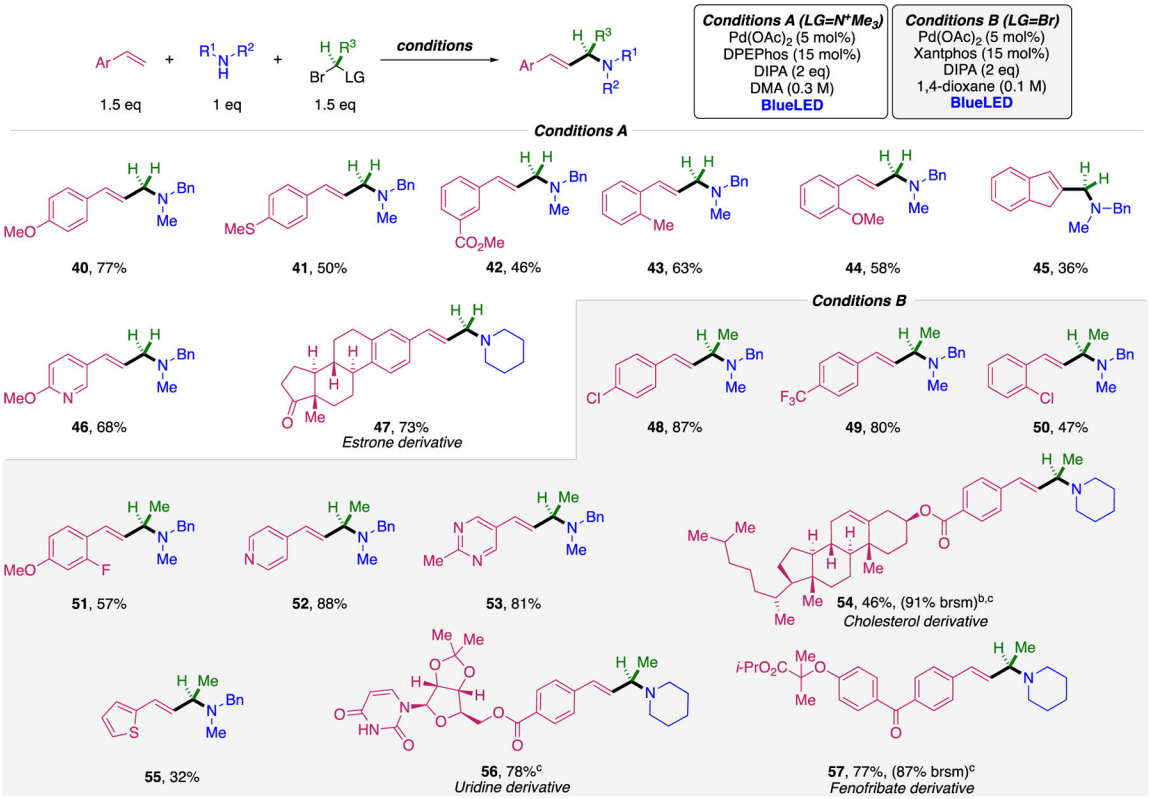
Scheme 1.



Scheme 2.

Scope of Amines[a]

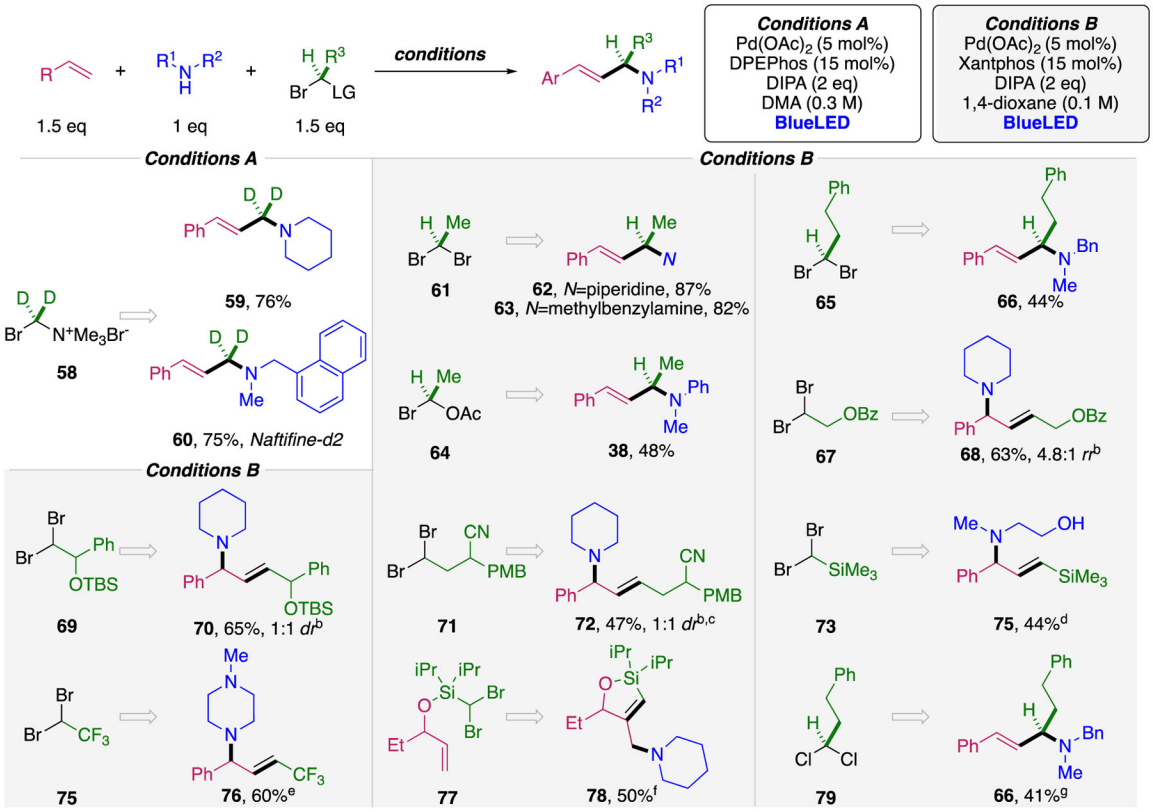
[a]0.4 mmol scale. [b]Amine·HCl salt used, 3 equiv of base. [c]Amine·HCl·hydrate used, 3 equiv of base. [d]0.2 mmol scale.



Scheme 3.

Scope of Alkenes[a]

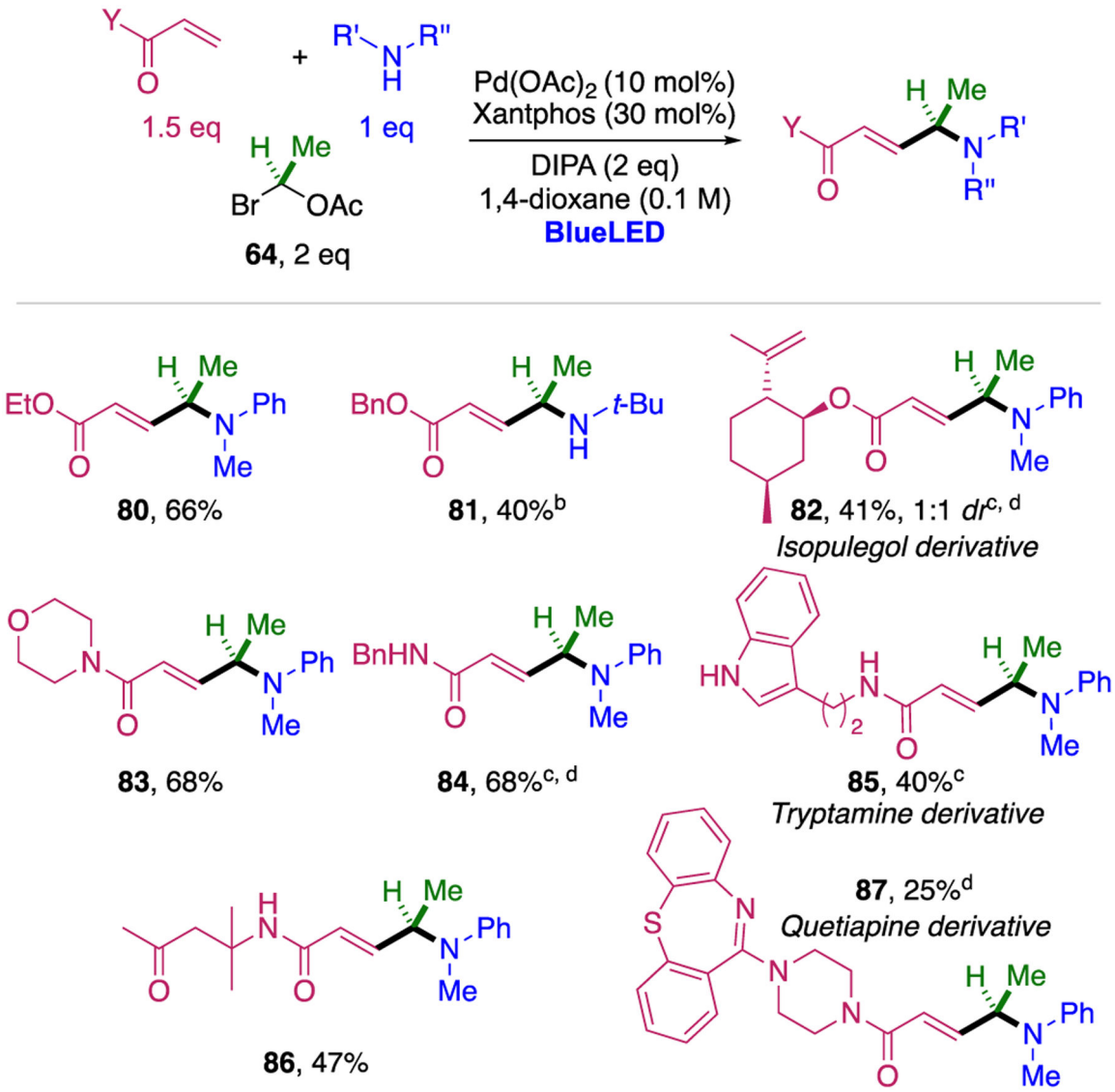
[a]0.4 mmol scale. [b]0.2 mmol scale. [c]1 equiv of alkene, 1.2 equiv of amine.



Scheme 4.

Scope of Dielectrophiles[a]

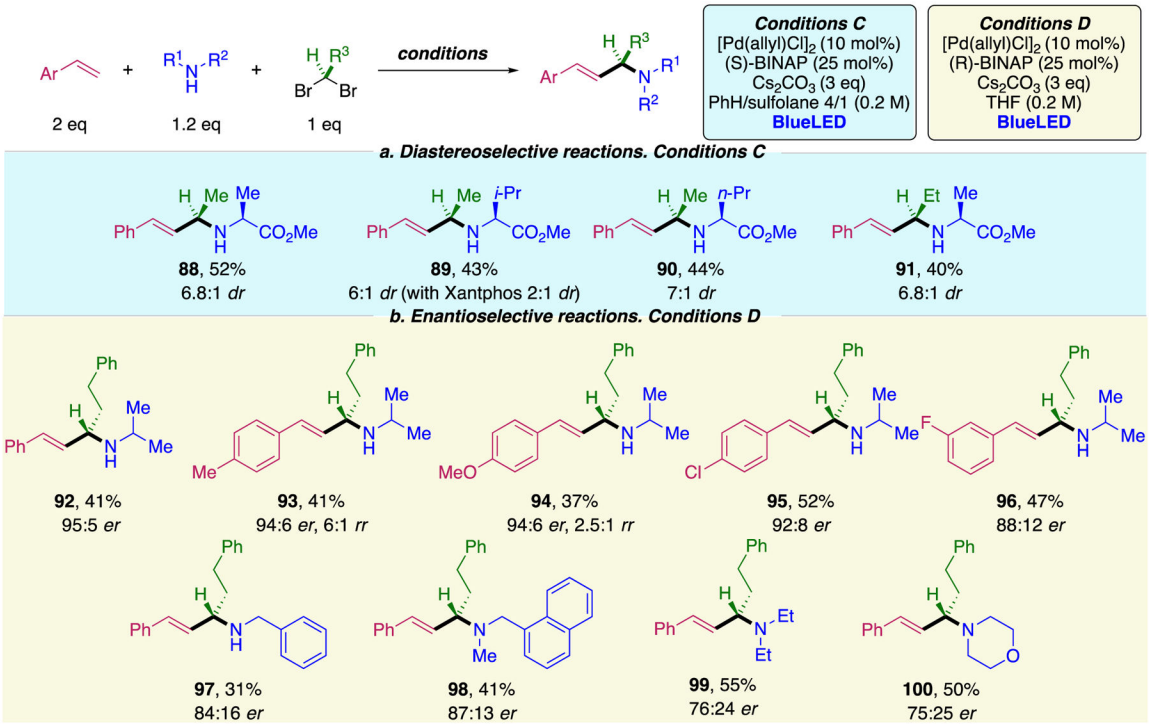
[a]0.4 mmol scale. [b]1.2 equiv of dibromide. [c]0.2 mmol scale. [d]***Conditions B***, 0.3 M. [e]***Conditions B***, DMA as solvent. [f]1 equiv of dibromide, 1.2 equiv of piperidine. [g]0.2 mmol scale, 1 equiv of amine, 1.5 equiv of styrene, 1.2 equiv of dichloride, $Pd(OAc)_2$ 5 mol %, PPh_3 30 mol %, 1 equiv of tetrabutylammonium bromide, 2 equiv of diisopropylamine, DMA (0.3 M).



Scheme 5.

Scope of Acrylic Esters and Amides[a]

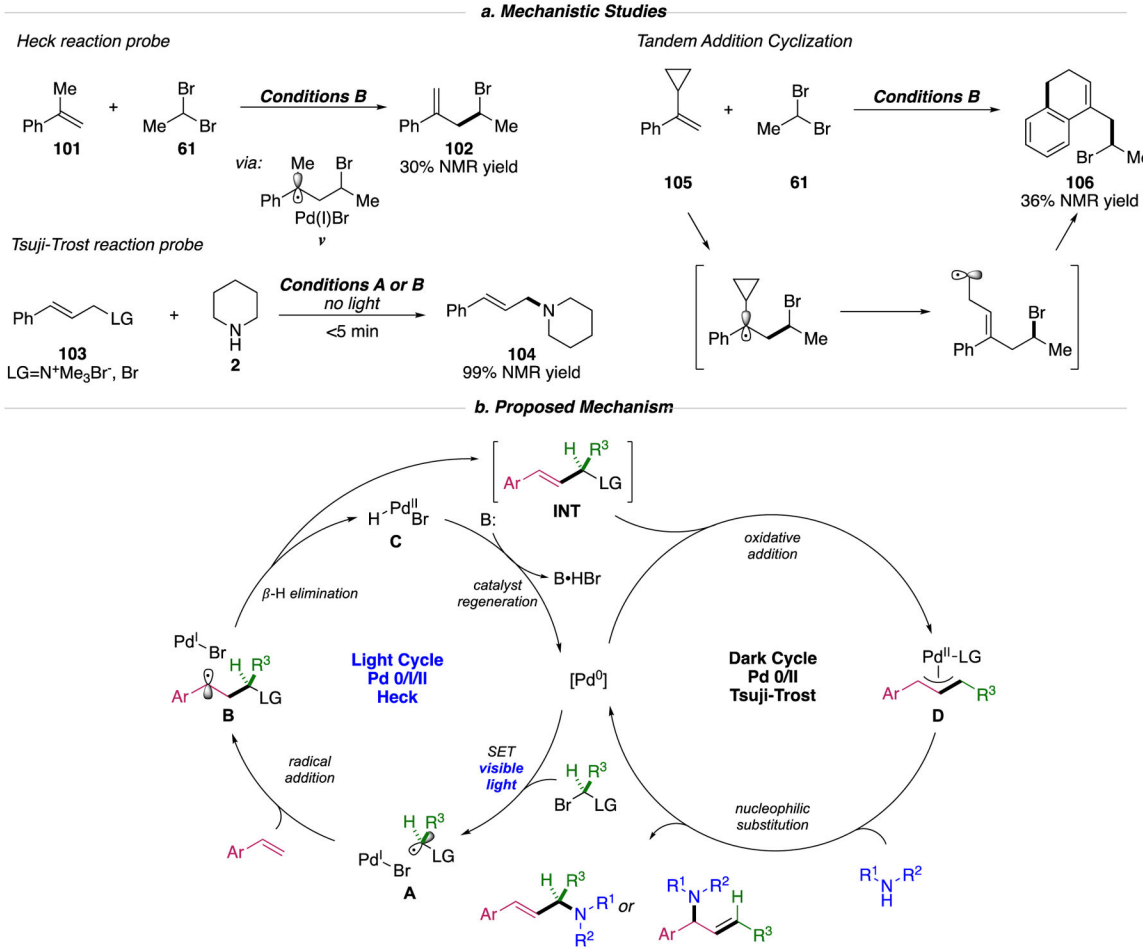
[a]0.3 mmol scale. [b]**61** used as a dielectrophile. [c]0.1 mmol scale. [d]1 equiv of alkene.



Scheme 6.

Stereoselective Examples[a]

[a]0.1 mmol scale.

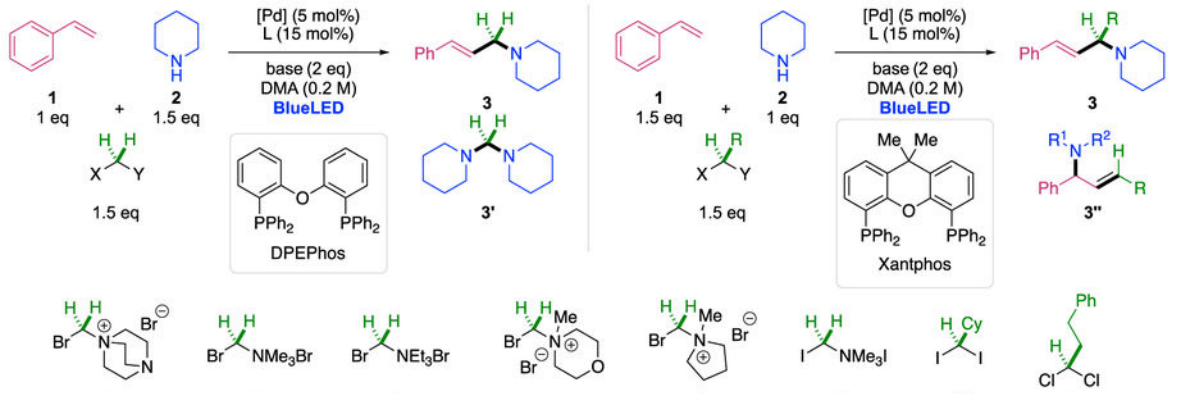


Scheme 7.
Elucidation of Mechanism

J Am Chem Soc. Author manuscript; available in PMC 2024 August 23.

Table 1.

Reaction Optimization[a]



Entry	[Pd]	L	base		Yield of 3, %[b]
1	$Pd(PPh_3)_4$	-	Cs_2CO_3	CH_2Br_2	traces[c]
2	$Pd(PPh_3)_4$	-	Cs_2CO_3	**4**	24
3[d]	$Pd(OAc)_2$	PPh_3	DIPEA	**5**	43
4[d]	$Pd(OAc)_2$	PPh_3	DIPEA	**6**	28
5[d]	$Pd(OAc)_2$	DPEPhos	DIPEA	**5**	63
6[e,f]	$Pd(OAc)_2$	DPEPhos	DIPA	**5**	75
7[e]	$Pd(OAc)_2$	DPEPhos	DIPA	**5**	0[g]
8[e]	$Pd(OAc)_2$	DPEPhos	DIPA	**7-9**	70-75

Entry	[Pd]	L	base		Yield of 3, %[b,h]
9	$Pd(OAc)_2$	DPEPhos			10
10[i]	$Pd(OAc)_2$	DPEPhos			25
11[i]	$Pd(OAc)_2$	PPh_3		$MeCHBr_2$	traces
12[i]	$Pd(OAc)_2$	Xantphos	DIPA		90 (4:1)
13[i,j,k]	$Pd(OAc)_2$	Xantphos			90 (9:1)
14[i,j]	$Pd(OAc)_2$	Xantphos			0[g]
15[i,j]	$Pd(OAc)_2$	DPEPhos		**10**	0[l]
16[i,j]	$Pd(OAc)_2$	DPEPhos		**11**	0

[a] 0.1 mmol scale.

[b] GC–MS yield, pentadecane as internal standard.

[c] **3′** major side product.

[d] 1.1 equiv of styrene, 1 equiv of piperidine.

[e] 1.5 equiv of styrene, 1 equiv of piperidine, 0.3 M concentration.

[f] ***Conditions A***.

[g] No light.

[h] In parenthesis ratio **3:3″**.

[i] 1,4-Dioxane as solvent.

[j] 0.1 M concentration.

[k] ***Conditions B***.

[l] **10** completely decomposed.